UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/731,905	12/10/2003	Nandan P. Koppiker	PC10332C	5794

28523 7590 05/21/2008

PFIZER INC.
PATENT DEPARTMENT, MS8260-1611
EASTERN POINT ROAD
GROTON, CT 06340

EXAMINER	
HENLEY III, RAYMOND J	
ART UNIT	PAPER NUMBER
1614	

NOTIFICATION DATE	DELIVERY MODE
05/21/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

~IPGSGro@pfizer.com

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte NANDAN P. KOPPIKER and ELIOT R. FORSTER

Appeal 2008-0407
Application 10/731,905
Technology Center 1600

Decided: May 19, 2008

Before DONALD E. ADAMS, ERIC GRIMES, and RICHARD M. LEBOVITZ, *Administrative Patent Judges*.

GRIMES, *Administrative Patent Judge.*

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 involving claims to a pharmaceutical composition, which the Examiner has rejected as obvious. We have jurisdiction under 35 U.S.C. § 6(b). We affirm.

BACKGROUND

"Neuropathy is a general term which describes a disease process which leads to the dysfunction of the nervous system. There are many causes of neuropathy affecting both the autonomic and peripheral nervous systems, such as metabolic disorders e.g. diabetes" (Spec. 1). Treatment of diabetic neuropathy focuses on providing pain relief (*id.* at 12: 33 to 14: 3).

The Specification discloses "the use of cyclic guanosine 3', 5'-monophosphate phosphodiesterase type five (cGMP PDE5) inhibitors, including in particular the compound sildenafil, for the treatment of neuropathy, including in particular the treatment of diabetic neuropathy" (*id.*).

DISCUSSION

1. CLAIMS

Claims 17-34 are pending and on appeal. Claims 17 and 27 are representative and read as follows:

> Claim 17: A combination comprising
> a therapeutically effective amount of a cGMP PDE5 inhibitor and
> a therapeutically effective amount of pregabalin or gabapentin.

> Claim 27: A method of treating neuropathy in a patient suffering therefrom which comprises administering a patient in need of therapy thereof a therapeutically effective amount of a combination of a cGMP PDE5 inhibitor and pregabalin or gabapentin.

2. OBVIOUSNESS

Claims 17-34 stand rejected under 35 U.S.C. § 103(a) as obvious in view of Yamasaki, [1] Ellis, [2] Singh, [3] Bueno, [4] and Stedman's Medical Dictionary.[5] The claims have been argued in four groups: claims 17-20 and 22-26 (Group 1), claim 21 (Group 2), claims 27-31, 33, and 34 (Group 3),

---

[1] Yamasaki, US 6,166,219, Dec. 26, 2000.
[2] Ellis et al., WO 94/28902, Dec. 22, 1994.
[3] Singh, WO 98/03167, Jan. 29, 1998.
[4] Bueno et al., US 6,127,418, Oct. 3, 2000.
[5] *Stedman's Medical Dictionary*, 22nd ed., published 1972 by The Williams & Wilkins Company, (Baltimore), pg. 1000, "polyneuropathy".

and claim 32 (Group 4). The claims in each group stand or fall together. 37 C.F.R. § 41.37(c)(1)(vii).

The Examiner relies on Yamasaki as disclosing "a pharmaceutical composition comprising a cGMP PDE5 inhibiting benzimidazole compound" having a specific formula, and "a method of treating a disorder that is responsive to treatment with a cGMP PDE5 inhibiting compound by administering an effective amount" of the compound (Ans. 3). The Examiner further finds that Yamasaki also discloses "various medical conditions which are responsive to treatment with the cGMP PDE5 inhibiting compounds, including diabetic neuropathy" (*id.* at 4).

The Examiner finds that Yamasaki does not teach the cGMP PDE5 inhibitor in combination with gabapentin or pregabalin, as in claims 17 and 27, but relies on Singh as disclosing "the use of gabapentin or . . . pregabalin … for the treatment of diabetic neuropathy" (*id.* at 5).

The Examiner concludes that it would "have been obvious to a person of ordinary skill in the art to employ either gabapentin or pregabalin in combination with a cGMP PDE5 inhibiting composition as disclosed by Yamasaki … because each compound was known in the art to be successful for achieving the same therapeutic effect" (*id.*). The Examiner finds that "[m]otivation to administer both compounds flows logically from the efficacy of each compound in treating diabetic neuropathy as demonstrated in the prior art and further, because each compound has been previously administered for this same therapeutic objective, at least additive results would have been … expected" (*id.*).

The Examiner relies on Ellis for disclosing dependent claim limitations, as discussed below. The Examiner also relies on Stedman's Medical Dictionary for disclosing limitations of dependent claims that have not been argued separately.

We conclude that the Examiner has set forth a prima facie case that claims 17 and 27 would have been obvious to the ordinary artisan. Yamasaki discloses benzimidazole compounds having a specific formula (I) (Yamasaki, abstract). Yamasaki also discloses that the "benzimidazole derivatives … are effective for preventing and treating various disorders … based on their blood sugar level-depressing activity," as well as for treating "diabetic complications (e.g., . . . diabetic neuropathy, diabetic cataract, diabetic retinopathy, etc.) … based on their cGMP-PDE (especially PDE-V)-inhibiting activity" and other activities (*id.* at col. 35, ll. 22-63).

Singh discloses that gabapentin and pregabalin are effective analgesics (Singh,[6] p. 2, ll. 17-18; p. 9, ll. 12-13) and suggests that compounds of the invention, preferably pregabalin, can be used to treat chronic pain disorders such as diabetic neuropathy (*id.* at p. 1, l. 17 to p. 2, l. 18).

We agree with the Examiner that it would have been prima facie obvious to one of skill in the art at the time the invention was made to combine the teachings of the cited references and thereby arrive at the invention of claims 17 and 27. Given the explicit teaching in the cited art

---

[6] Singh refers to pregabalin as 3-aminomethyl-5-methyl-hexanoic acid and (S)-3-(aminomethyl)-5-methylhexanoic acid (Singh, p. 2, ll. 17-18). Bueno discloses that these compounds are "known generically as pregabalin" (Bueno at col. 2, ll. 51-53).

that pregabalin, gabapentin, and a cGMP PDE5 inhibitor can all be used to treat the same condition (i.e., diabetic neuropathy), persons of ordinary skill in the art would have reason to have combined the claimed compounds to treat diabetic neuropathy for their expected additive effects. As shown by the Specification's working example (Spec. 12-14), it was known that treatment of diabetic neuropathy focuses on pain relief, and it is well-known to combine pain relievers to achieve more effective pain relief.

Appellants argue that there was no motivation in the art to combine the recited compounds because, in Yamasaki, "it is clear that the treatment of diabetic neuropathy by the benzimidazole compounds could be mediated by some other listed mechanism of action(s) (e.g., smooth muscle cell suppressing activity or yet another cGMP PDE isoform)" (App. Br. 7). Appellants further argue that Yamasaki "never *directly* links the two i.e., cGMP PDE5 inhibition and diabetic neuropathy," and that "[w]hile Yamasaki … discloses cGMP PDE5 and separately diabetic neuropathy, any connection between the two is confounded by other confusing and/or conflicting … statements" (*id.*).

We are not persuaded by this argument. As set forth above, Yamasaki expressly discloses that the disclosed benzimidazole compounds can be used to treat diabetic neuropathy, among other things, "based on their cGMP-PDE (especially PDE-V)-inhibiting activity, smooth muscle relaxing activity, bronchodilating activity, vasodilating activity, smooth muscle cell suppressing activity, and antiallergic activity" (Yamasaki, col. 35, ll. 52-55). Appellants' argument, as we understand it, is that, based on this disclosure, one of ordinary skill in the art could not reasonably conclude that the use in

treating diabetic neuropathy was attributable to the "cGMP-PDE (especially PDE-V)-inhibiting activity," as opposed to one of the other listed activities.

In our view, however, the evidence of record supports the Examiner's position (Ans. 9) that the physiological effects listed by Yamasaki ("smooth muscle relaxing activity, bronchodilating activity," etc.) are the result of the biochemical effect of inhibiting cGMP PDE5 activity. For example, Yamasaki states that "[b]ecause of their blood sugar-depressing effect or PDE5 inhibitory effect," the disclosed compounds are useful for treating diabetic complications, among other disorders (Yamasaki, abstract). The same statement is repeated in addressing "Industrial Applicability" (*id.* at col. 164-165). Yamasaki does not mention smooth muscle relaxing activity, bronchodilating activity, etc. at either place, supporting the Examiner's position that the physiological effects listed in column 35 are merely the result of inhibiting cGMP PDE5.

Further evidence supporting the Examiner's position is provided by Ellis, which states that inhibition of cyclic guanosine 3',5'-monophosphate phosphodiesterases (cGMP PDEs)

> leads to elevated cGMP levels which, in turn, provides the basis for . . . treatment of stable, unstable and variant (Prinzmetal) angina, hypertension, pulmonary hypertension, congestive heart failure, atherosclerosis, conditions of reduced blood vessel patency e.g. post-percutaneous transluminal coronary angioplasty (post-PTCA), peripheral vascular disease, stroke, bronchitis, allergic asthma, chronic asthma, allergic rhinitis, glaucoma, and diseases characterised by disorders of gut motility, e.g. irritable bowel syndrome (IBS).

(Ellis 2.) Ellis also discloses that cGMP PDE inhibitors "are useful in the treatment of erectile dysfunction" (*id.*).

Many of the disorders listed by Ellis as being treatable based on cGMP PDE inhibition are also listed by Yamasaki as being treatable "based on their cGMP-PDE (especially PDE-V)-inhibiting activity, smooth muscle relaxing activity, bronchodilating activity, vasodilating activity, smooth muscle cell suppressing activity, and antiallergic activity." The overlapping disorders include

- hypertension (Yamasaki, col. 35, l. 36),
- pulmonary hypertension (*id.* at col. 35, l. 37),
- congestive heart failure (*id.*),
- atherosclerosis (*id.* at col. 35, l. 40),
- restenosis after PTCA (compare to Ellis' "conditions of reduced blood vessel patency e.g. . . . post-PTCA")(Yamasaki, col. 35, l. 51),
- cerebral apoplexy (compare to Ellis' "stroke")(*id.* at col. 35, l. 42),
- bronchitis (*id.* at col. 35, l. 43),
- allergic asthma (*id.*),
- chronic asthma (*id.*),
- allergic rhinitis (*id.* at col. 35, l. 44),
- glaucoma (*id.*),
- diseases characterized by enteromotility disorders (compare to Ellis' "diseases characterised by disorders of gut motility")(Yamasaki, col. 35, l. 44-45), and
- impotence (compare to Ellis' "erectile dysfunction")(Yamasaki, col. 35, l. 46).

The overlapping disorders include some that would appear to be treated by agents having bronchodilating activity (chronic asthma), vasodilating activity (hypertension), smooth muscle cell suppressing activity (restenosis after PTCA), and antiallergic activity (allergic asthma, allergic

rhinitis). Our conclusion that all of the physiological effects listed by Yamasaki result from the biochemical effect of inhibiting cGMP PDE inhibition is supported by the substantial overlap between the disorders listed by Ellis as being treatable based on cGMP PDE inhibition and those listed by Yamasaki as being treatable based on "cGMP-PDE (especially PDE-V)-inhibiting activity, smooth muscle relaxing activity," etc. Our conclusion is also supported by the fact that treatment of the disorders listed by Ellis reasonably appear to require one of the physiological effects listed by Yamasaki such as bronchodilation, vasodilation, etc. We therefore agree with the Examiner that one of ordinary skill in the art would have understood Yamasaki to disclose treating diabetic neuropathy with compounds having "cGMP-PDE (especially PDE-V)-inhibiting activity."

Appellants also argue that the Examiner has not established a prima facie case of obviousness (App. Br. 6). In particular, Appellants argue that the Yamasaki "passages relied on by the Examiner are simply a classic invitation to experiment to determine which disease/condition should be linked with a particular mechanism of action" (*id.* at 7). Appellants further argue that "drug combinations may have drug-drug interactions, and it is the unpredictability of such drug-drug interactions that is an important aspect of the lack of a reasonable expectation of success" (*id.* at 8).

We are not persuaded by this argument. "Obviousness does not require absolute predictability of success. . . . For obviousness under § 103, all that is required is a reasonable expectation of success." *In re O'Farrell*, 853 F.2d 894, 903-04 (Fed. Cir. 1988). In the instant case, Singh suggests pregabalin or gabapentin for treating diabetic neuropathy and demonstrates

that the compounds have pain relieving effect in an animal model. Yamasaki expressly suggests treating diabetic neuropathy with a compound that is a cGMP PDE5 inhibitor. Although specific examples demonstrating the treatment of diabetic neuropathy or other pain are not provided by Yamasaki, such specific demonstrations are not required. "In patent prosecution, the examiner is entitled to reject application claims [in view of] a prior art patent without conducting an inquiry into whether or not that patent is enabled. . . . The applicant, however, can then overcome that rejection by proving that the relevant disclosures of the prior art patent are not enabled." *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1355 (Fed. Cir. 2003). Thus, "a presumption arises that both the claimed and unclaimed disclosures in a prior art patent are enabled" (*id.*).

In view of the pain relief demonstrated in Singh and the presumption of enablement that applies to the disclosure of Yamasaki, and the absence of any evidence rebutting that presumption, we find that one of skill in the art would have had a reasonable expectation of success in treating neuropathy using a combination of a cGMP PDE5 inhibitor and pregabalin or gabapentin. While we acknowledge that drug-drug interactions may occur, an absolute predictability of success is not required, but only a reasonable expectation of success. Thus, even in view of the possibility of drug-drug interactions, the prior art supports a reasonable expectation of success for the claimed invention.

Claims 21 and 32, which Appellants argue separately, are directed to a composition and method, respectively, that are similar to those of claims 17 and 27, respectively, but require that the cGMP PDE5 inhibitor is sildenafil.

With regard to claims 21 and 32, the Examiner finds that Yamasaki does not "expressly teach the use of the cGMP PDE5 inhibitor sildenafil …. as a compound for treating diabetic neuropathy" (Ans. 6). The Examiner relies on Ellis as disclosing that sildenafil is "a potent and selective inhibitor of cGMP-specific PDE5" (*id.*).[7]

The Examiner concludes that "it would have been an obvious conclusion to one of ordinary skill in the art that the treatment of a condition known to be responsive to a cGMP PDE5 inhibiting agent would not be solely limited to those compounds disclosed by Yamasaki …, but that effective treatment of such a condition would have been reasonably expected to occur with any one or more other compounds known to exert the same effect (i.e., the inhibition of cGMP PDE5)" (*id.*). The Examiner further concludes that it would have been obvious to use sildenafil to treat diabetic neuropathy because sildenafil "was well known in the art to exert inhibitory effects on cGMP-PDE5 and … would have been reasonably expected to demonstrate the same, or substantially similar, efficacy in treating diabetic neuropathy, as that shown by the benzimidazole cGMP-PDE inhibiting compounds" of Yamasaki (*id.*).

We conclude that the Examiner has set forth a prima facie case that claims 21 and 32 would have been obvious to the ordinary artisan. Ellis discloses pyrazolopyrimidinones for the treatment of impotence (Ellis,

---

[7] The Examiner relies on the instant Specification as establishing that the compound referred to by Ellis as 5-[2-ethoxy-5-(4-methyl-1-piperazinylsulphonyl)-phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one is also known as sildenafil (*id.*; citing the Spec. at pg. 1, ll. 12-13).

abstract). Ellis also discloses that one of the preferred compounds is sildenafil (*id.* at pg. 7, ll. 1-3). Ellis also discloses that sildenafil is an inhibitor of cGMP PDE5 (*id.* at pg. 9, last para.). We agree with the Examiner that Ellis's teaching that sildenafil is a potent inhibitor of cGMP PDE5 would have reasonably suggested to one of skill in the art substituting sildenafil for the benzimidazole compounds of Yamasaki in the method suggested by the references of treating neuropathy using a combination of a cGMP PDE5 inhibitor and pregabalin or gabapentin.

Appellants argue that there is nothing to motivate the particular selection of sildenafil (or its pharmaceutically acceptable salts) from among cGMP inhibitors (Appeal Br. 6).

We are not persuaded by this argument. In view of the Examiner's well-stated arguments set forth above, we agree that the references as a whole suggest the substitution of the cGMP PDE5 inhibitor sildenafil of Ellis for the cGMP PDE-inhibiting benzimidazoles of Yamasaki, and thus suggest the claimed invention.

SUMMARY

The Examiner's rejection is supported by the preponderance of the evidence of record. We therefore affirm the rejection of claims 17-34 under 35 U.S.C. § 103.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED

lp

PFIZER INC.
PATENT DEPARTMENT, MS8260-1611
EASTERN POINT ROAD
GROTON CT 06340